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Request for grant of a patent

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1. [redacted] Reference — WPM/P6982GB

2. Patent application number *(The Patent Office will fill in this part)* — 9720590.0

3. Full name, address and postcode of the or of each applicant *(underline all surnames)* — MEDEVA EUROPE LIMITED
10 St. James's Street
London SW1A 1EF

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation — United Kingdom

4. Title of the invention — PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF INFLAMMATORY BOWEL DISEASE

5. Name of your agent *(if you have one)* — W.H. BECK, GREENER & CO.

"Address for service" in the United Kingdom to which all correspondence should be sent *(including postcode)*
7 STONE BUILDINGS
LINCOLN'S INN
LONDON
WC2A 3SZ

[redacted] Patents ADP number *(if you know it)* — 323001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day/month/year)*

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Number of earlier application	Date of filing *(day/month/year)*

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a) any applicant named in part 3 is not an inventor, or
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Continuation sheets of this form	
Description	20
Claim(s)	2
Abstract	
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Priority documents	
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Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination *(Patents Form 9/77)*	
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11. I/We request the grant of a patent on the basis of this application.

Signature [signature] Date 26.09.97

12. Name and daytime telephone number of person to contact in the United Kingdom. Mr W.P. McMunn - (0171) 405 0921

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PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF INFLAMMATORY BOWEL DISEASE

This invention relates to use of Xanthan gum, particularly in the form of enemas for the treatment of inflammatory bowel disease (IBD), and to orally administrable and rectally/vaginally administrable compositions containing Xanthan gum as the sole therapeutically active agent.

IBD covers chronic non-specific inflammatory conditions of the gastro-intestinal tract, of which the two major forms are Crohn's disease and ulcerative colitis. The aetiology of these diseases is uncertain. Many inflammatory mediators have been proposed including prostanoids, leukotrienes, platelet activating factor, cytokines, and free oxygen radicals. Although specific inhibitors of most of these have been tried in experimental models, the most effective drugs currently available for these diseases have a broad activity against inflammatory processes.

Crohn's disease is characterised by thickened areas of the gastro-intestinal wall, with inflammation extending through all layers, deep ulceration and fissuring of the mucosa, and the presence of granulomas. Affected areas may occur in any part of the gastro-intestinal tract, although the terminal ileum is frequently involved, and they may be interspersed with areas of relatively normal tissue. Fistulas and abscesses may develop. Symptoms depend on the

site of disease but may include abdominal pain, diarrhoea, fever, weight loss and rectal bleeding.

In ulcerative colitis, disease is continued to the colon and rectum. Inflammation is superficial but continuous over the affected area and granulomas are rare. In mild disease, the rectum alone may be affected (proctitis). In severe disease ulceration is extensive and much of the mucosa may be lost, with an increased risk of toxic dilatation of the colon, a potentially life-threatening complication.

Abdominal colectomy with mucosal proctectomy and ileal pouch-anal anastomosis is the preferred treatment for most patients with ulcerative colitis who require surgery. Pouchitis, the most common long-term complication of the procedure, occurs in up to 49% of patients at 10 years. Chronic pouchitis is distinguished from acute pouchitis by duration of symptoms for more than 4 weeks. The aetiology of pouchitis is unknown but it appears that both a history of ulcerative colitis and increased bacterial concentrations (relative to the normal ileum) are factors.

Currently, there is no satisfactory treatment for patients with chronic pouchitis who fail to respond to empiric antibiotic therapy. Although metronidazole is effective in some patients, long-term use is limited by concerns for neurotoxicity with peripheral neuropathy.

Numerous compounds have been examined in the last twenty years to find effective measures for the treatment of IBD. Such compounds include azathioprine, arsenicals, disodium cromoglycate, metronidazole, lignocaine, 5-aminosalicyclic acid (5-ASA), fish oils, thalidomide and cyclosporin. In EP-A-0351987, carbomer was proposed for treating IBD. The wide diversity of treatments, however, is an indication of the complexity and intransigence of this condition.

The inventors have now found that a polysaccharide (hydrogels/gums), in particular Xanthan gum in therapeutic amounts is effective for the treatment of IBD.

This is surprising, since the polysaccharide gums/hydrogels such as Xanthan gum with its cellulostic backbone are normally thought to be inert. On the other hand, high doses of the polysaccharides can be used with minimal side effects.

Although Xanthan gum and other polysaccharide gums have been present as a thickening agent in enemas used to treat IBD (for example, Xanthan gum in WO-A-9603115), it was never realised that they also had pharmacologically active properties for treatment of the disease. Furthermore in EP-A-620012 (US-A-5518711), Xanthan gum is used at 0.15-0.6 w/v% in a X-ray contrast medium administered to the colon to detect Crohn's disease. Again, however, there is no report of it also treating the disease.

In US-A-5380522 a medicament of an anion-binding polymer and a hydrophilic polymer was used to alleviate irritable bowel syndrome. Xanthan gum was one of a number of compounds mentioned under anion-binding polymer, but is was not used in the examples.

Accordingly in a first aspect of the invention there is provided the use of a polysaccharide (hydrogel/gum) as a therapeutically active agent in the preparation of a medicament for the treatment or prophylaxis of IBD.

In a second aspect of the invention there is provided a rectally or post-gastrically delayed release oral (DRO) administrable pharmaceutical composition comprising a polysaccharide gum as the sole therapeutically active agent together with a pharmaceutically acceptable carrier or vehicle.

In a third aspect of the invention there is provided the use of a polysaccharide gum as the sole therapeutically active agent in the manufacture of a medicament for the treatment or prophylaxis of IBD.

In yet another aspect of the invention there is provided a method for the treatment or prophylaxis of IBD comprising contacting the diseased mucosa of the gastro-intestinal tract with a polysaccharide gum.

Suitable polysaccharide gums for use in the invention are the naturally occurring high molecular weight polysaccharide gums and chemically modified derivatives thereof. Examples are as follows:

Xanthan gum, Sodium carboxymethyl cellulose, Tragacanth, Methylcellulose, Sodium alginate, Hydroxypropylmethylcellulose, Karya gum, Methylethylcellulose, Soluble starch, Pectin, Propylene glycol alginate, Hydroxy ethyl cellulose, Guar gum, Carra geenan, Agar gum, and Gum acacia (arabic).

Preferably the polysaccharide is water soluble. In a preferred form of the invention, the polysaccharide is Xanthan gum.

Xanthan gum (CAS registry no. 1138-66-2) is monographed at USP NF XVI p161 and is described as a high molecular weight polysaccharide gum produced by a pure-culture fermentation of a carbohydrate with Xanthomonas campestris. It contains D-glucose and D-mannose as the dominant hexose units, along with D-glucuronic acid and is prepared as the sodium, potassium or calcium salt.

Suitable pharmaceutically acceptable salts of the aforementioned polysaccharides are also within the scope of the invention and include alkali metals (e.g. sodium potassium) and alkaline earth metals (e.g. calcium or barium).

When a polysaccharide, such as Xantham gum is present as the sole active agent, then no other therapeutically active agent such as 5-ASA or corticosteriods would be present.

Optionally, however, other therapeutic agents currently used or proposed for treating IBD can also be used sequentially in a different dosage form or concomitantly in the same dosage form as the polysaccharide gum. Examples of other such therapeutic agents are 5-ASA, immune modifiers such as azathioprine, cyclosporine and FK506, corticasteroids such as prednisolone, budesonide and hydrocortisone, antibiotics such as metronidazole, ciprofloxacin, amoxicillin, tetracycline and sulphamethoxazole, and antidiarreals such as loperamide and codeine sulphate, and local anaesthetics such as lignocaine.

By IBD we mean Crohn's Disease and ulcerative colitis including ulcerative proctitis, ulcerative proctosigmoiditis, lymphocytic colitis, intractable distal colitis, ileocolitis, collagenous colitis, microscopic colitis, pouchitis, radiation colitis, and antibiotic-associated colitis. The invention has been found to be particularly useful in the treatment of pouchitis.

The polysaccharide may be incorporated into a pharmaceutical composition to be administered either or rectally, e.g. as an enema or foam enema, or orally, for

example, in coated tablets or capsules as described below. Also, the polysaccharide may be formed into microgranules and coated, for example with Eudragit-L or S and contained within a capsule similarly coated. In all solid compositions it is preferable to include a disintegrant. Still further, the polysaccharide may be formulated in a number of dosage forms, e.g. uncoated or coated solid dosage forms for non-delayed release or delayed release oral administration, for example using different polymers in the Eudragit product range.

According to a preferred embodiment of the present invention, the pharmaceutical composition takes the form of an enema formulation such as a liquid or foam enema which is vaginally or rectally administered to the lower colon. The enema formulations would comprise a polysaccharide gum such as Xanthan gum dissolved or dispersed in a suitable flowable carrier vehicle, such as deionised and/or distilled water. The formulation can be thickened with one or more thickeners, can contain a buffer, and can also comprise an effective amount of a lubricant such as a natural or synthetic fat or oil, e.g. a tris-fatty acid glycerate or lecithin. Non-toxic non-ionic surfactants can also be included as wetting agents and dispersants. Unit doses of enema formulations can be administered from pre-filled bags or syringes. In the case of a pressurised enema formulation the carrier vehicle may also comprise an effective amount of a foaming agent such as *n*-butane, propane or *i*-butane, or the foaming agent could be held separately from the

composition such as in a bag-in-can system. Enema foams may also comprise expanding agents and foam-stabilisers.

The viscosity of the enema is preferably 10,000 to 70,000 mPa.s more preferably 10,000 to 70,000 mPa.S and most preferably 10,000 to 40,000 mPa.S. The pH is preferably 3.5 to 7.5, preferably 6.5 to 7.5.

A preferred dosage for an enema is 200mg to 2000mg, more preferably 250mg to 1650mg, more preferably still 550 to 1000mg in an aqueous or non-aqueous carrier. The volume of the enema is typically 50ml to 200ml preferably about 100ml.

In a further embodiment of the invention, the polysaccharide gum is administered to the small intestine or colon of a patient by oral ingestion of a post-gastric delayed release (DRO) unit dosage form such as a tablet or capsule, comprising an effective amount of polysaccharide gum which is enterically coated so as to be released from the unit dosage form in the lower intestinal tract, e.g. in the ileum and/or in the colon of the patient. Enteric coatings remain intact in the stomach, but dissolve and release the contents of the dosage form once it reaches the region where the pH is optimal for dissolution for the coating used.

The DRO form may optionally also be formulated to give a sustained release of the polysaccharide gum. The delay

release can be obtained, for example, by complexing the polysaccharide gum with a polyacrylic acid derivative (a gum-polyacrylate complex) more particularly a gum-carbomer complex. Alternatively particles of the gum or gum complex could be incorporated into a hydrophobic matrix such as Gelucire™ (Gattefosse, France).

Aqueous film-coating technology is advantageously employed for the enteric coating of pharmaceutical dosage forms. A useful enteric coating is one that remains intact in the low pH of the stomach, but readily dissolves when the optimum dissolution pH of the particular coating is reached. This can vary between pH 3 to 7.5 depending on the chemical composition of the enteric coating. The thickness of the coating will depend on the solubility characteristics of the coating material and the site to be treated.

By delayed release we mean that release is substantially post-gastrically, and by sustained release we mean that the total release of the Xanthan gum is slow and sustained over a period of time, as opposed to being released as a bolus.

The majority of the release will be targeted to the part of the small intestine or colon where the active disease is prevalent and this varies for Crohn's disease and ulcerative colitis. Thus typically for an enteric coated capsule, the enteric coating should dissolve in the pH of the jejunum, ileum or colon.

Preferably the unit dosage of Xanthan gum in the delayed release oral composition is 200mg to 2000mg more preferably about 250mg to 1650mg, more preferably still 550mg to 1000mg.

The above also is approximate to the total daily dosage and can be achieved by one or more unit dosages taken once, twice, three or more times daily.

The DRO formulation can be provided in which an enteric coated capsule containing the polysaccharide gum has a coating , thickness of coating and dissolution profile described in EP-A-0097651 (the contents of which are incorporated herein by reference). Suitable coating include cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, ethyl cellulose or polyvinyl acetate phthalate but the preferred coating material is an anionic polymer, especially one having the dissolution profile specified in EP-A-0097651, optionally in admixture with a neutral insoluble but permeable polymer. The presently preferred anionic polymers are anionic carboxylic polymers, i.e. polymers in which the anionic groups are at least predominantly free carboxylic and/or esterified carboxylic groups. It is particularly preferred that the anion polymers should be acrylic polymers and the presently most preferred polymers are partly methyl esterified methacrylic acid polymers in which the ratio of free acid groups to ester groups is about 1:1 (i.e. Eudragit L), especially,

about 1:2 (i.e. Eudragit S), or a neutral polymer coating, more specifically poly(ethylacrylate-methylmethacrylate) (e.g. Eudragit NE30D).

A DRO formulation can also be achieved by coating a powder or microgranular formulation of a polysaccharide gum of the invention with coatings as mentioned above. The coated microgranules or material may then be compressed into tablets or packed into hard gelatin capsules suitable for oral administration. Suitable coatings and thicknesses to achieve this sustained release are also disclosed in EP-A-0572486 (incorporated herein by reference).

In general coating thicknesses of about 25 to 200 μm, and especially 75 to 150 μm, are preferred using about 3 to 25 mg, preferably 8 to 15 mg of acidic coating material per cm^2 of tablet or capsule surface. The precise coating thickness will however depend upon the solubility characteristics of the acidic material used and site to be treated.

In another preferred DRO or rectally administrable embodiment of the invention, sub 150µm particles of the polysaccharide gum or complex thereof (e.g. carbomer complex) is coated (partially or completely) or impregnated with a water insoluble anionic polymer. This prevents the formation of lumps and rather encourages the resulting hydrophobic particles of polysaccharide gum to disperse and coat the bowel wall when the contents of the DRO tablet or

capsule are released. This technology is described in more detail in international application no. PCT/GB97/01847 (incorporated herein by reference).

By sub 150μm particles, we mean such that 100% of particles in the DRO will pass through a 150μm sieve. It is preferred that 100% of the hydrophillic carbomer particles pass a 100 μm sieve screen (i.e. they are sub 100 μm), more preferably at least 90%, especially at least 95%, of the hydrophilic particles pass a 63 μm sieve screen, more preferably a 50 μm sieve screen. The precise particle size must be small enough to provide a composition with a suitable degree of hydrophobicity following coating with the anionic polymer. Preferred particle size may vary according to the nature and amount of the cation present in the complex and the nature and amount of the anionic polymer.

The presently preferred anionic polymers are anionic carboxylic polymers, i.e. polymers in which the anionic groups are at least predominantly free carboxylic and/or esterified carboxylic groups. It is particularly preferred that the anionic polymer is an acrylic polymer and the presently most preferred polymers are partly methyl esterified methacrylic acid polymers such as poly(methacrylic acid, methyl methacrylate) in which the ratio of free acid groups to ester groups is about 1:1 ((e.g. those available from Röhm Pharma GmbH under the Trade Mark EUDRAGIT L), or especially, about 1:2 ((e.g. those available from Röhm Pharma GmbH under the Trade Mark

EUDRAGIT S). In this connection, selection of a particular anionic polymer and the amount thereof can provide the hydrophilic particles with a desired dissolution profile.

The amount of anionic polymer used will depend upon the nature and amount of the cation present in the salt, the nature of the impregnating anionic polymer, and the degree of hydrophobicity required. A suitable amount can be determined by simple experimentation but usually the anionic polymer will be present in an amount of 10 to 50%, preferably 20 to 40, more preferably 25 to 35 and especially about one third, based on the weight of the carbomer complex. Having regard to the small particle size the amount of polymer will be less than the theoretical amount required to coat the particles, and the swelling and dissolution of the carbomer will not be controlled by pH.

The polysaccharide particles are impregnated/ hydrophobised by milling and passing through a suitable sieve (as aforementioned), stirring the sieved particles into a mixture of e.g. isopropanol and water (solvent) and partly methyl esterified methacrylic acid polymer (e.g. Eudragit S100) at from 20 to 40% by weight of the polysaccharide particles (the solvent/coating solution having previously been agitated until clear), stirring then evaporating the solvent under vacuum at about 50-70° to leave coated polysaccharide particles. Thereafter the resulting powder can be filled into gelatin capsules ready for enteric coating.

The invention will now be described by way of the following examples.

Example 1

Foam Enema Formulation

14,871g of purified water containing 22g of dissolved methyl paraben and 2g of dissolved propyl paraben as preservatives were placed in a 20 litre Moltomat-Universal MMU 20 homogenizer. Then 435g of Xanthan gum Keltrol TF having a water content of 7.6% (form the Company Kelco) were dispersed in the preserved water under efficient homogenization and reduced pressure.

30g of unbleached lecithin were then added and dispersed under homogenization and reduced pressure. At this stage the pH of the viscous gel obtained was 6.3. A solution then made of 0.45 g sodium hydroxide pellets and 20g of water was added and dispersed under reduced pressure. The pH then was 6.93. Finally 155g of Polysorbate 80 (non-ionic surfactant) and 4g of Citral (perfume) were added and dispersed under reduced pressure.

The final foam enema appeared as a slightly hazy gel, having a pH of 7.04 and a viscosity of 40'000 mpa.s at 20°C as measured using a Brookfield DV II viscometer (1.5 rpm, spindle 63).

A foam enema was then produced using this formulation by adding 2.2g of n-butane per 100g of the above formulation in a pressurised mixing unit and the mixture was then filled into bag-in-can aerosol canisters. Each canister contained 23g of the mixture from which 21g of foam was delivered through a valve and an applicator, i.e. about 530 mg of Xanthan gum per delivered dose.

Liquid Enema Formulation

To 4,906g of purified water containing 10g of dissolved methyl paraben and 2g of dissolved propyl paraben used as preservatives, 58.95g of Xanthan gum Keltrol TF containing 6.7% water (i.e. 55g dry basis) was added in an homogenizer and dispersed under efficient homogenization under reduced pressure. The pH of the gel obtained was 6.05 and the viscosity was 7,500 mPa.s (22°C - 1.5 rpm-spindle 63 - Brookfield DV II). At this stage 23g of sodium citrate. $2H_2O$ was added as buffering agent. The pH went up to 7.15 and the viscosity 40,000 mPa.s measured as above. The formulation, which appears as a slightly hazy gel, was then packed into a bag-in-can canister equipped with a valve and an applicator and pressurised with nitrogen. If the bag of the bag-in-can system is filled with 104g of the formulation above then 100g of the formulation can be delivered through the valve and applicator corresponding to a dose of 1.1g of Xanthan gum.

Example 2

The enema of Example 1 was then given to patients. The patients were twenty adults who had previously undergone total colectomy with mucosal proctectomy and ileal J-pouch anal anastomosis for ulcerative colitis and who had active chronic pouchitis refractory to standard therapy. Patients had chronic pouchitis, as defined as continuous symptoms of pouchitis for more than 4 weeks and a Pouchitis Disease Activity Index (PDAI) score of at least 7 points on an 18 point scale. All patients had either failed or were intolerant to metronidazole as well as other commonly used treatments for pouchitis. Mucosal inflammation, determined by endoscopic examination, was limited to the pouch and did not extend into the ileum proximal to the pouch.

The demographics of the patients entered into the study are presented in Table 1. There were no significant differences in the age, gender distribution, smoking history, time since the diagnosis of ulcerative colitis, duration of pouch function, time since the first episode of pouchitis, duration of the current episode of pouchitis, or in the medications previously used for treatment of pouchitis. All patients had been on medication for pouchitis, previously, and one half of the patients were on concurrent treatment for chronic pouchitis (Table 2).

TABLE 1

PATIENT CHARACTERISTICS

Number of Patients	20
Age (mean)	40(18-62)
Number of Men:Women	12:8
Number of Cigarette Smokers, current:former:never	1:2:17
Years since diagnosis of Ulcerative colitis. Median (range)	9(3-32)
Months of pouch function. Median (range)	45(4-161)
Months since the first episode of pouchitis. Median (range)	42(3-151)
Months of current pouchitis episode. Median (range)	4(.8-151)

TABLE 2

THERAPY FOR POUCHITIS (20 PATIENTS)

Therapy	No. Of Patients Current	Previous
Antibiotics		
Metronidazole	3	16
Ciprofloxacin	6	15
Amoxicillin/clavulanic acid	1	6
Tetracycline	0	3
Trimethoprine/sulfamethoxazole	1	0
5-ASA		
Sulfasalazine	1	5
Oral mesalamine	0	5
Mesalamine enemas	0	3
Mesalamine suppositories	0	3
Corticoseroids		
Prednisone	1	7
Hydrocortisone enemas	0	5
Immune Modifiers		
Azathioprine	0	0
Cylcosporine	0	0
FK506	0	0
Antidiarrheals		
Loperamide	5	3
Codeine sulfate	0	1

TABLE 3

DISEASE ACTIVITY AT BASELINE AND COMPLETION OF TREATMENT WITH XANTHAN GUM ENEMA

	Baseline Median (range)	Completion Median (range)
Clinical Score	4(1,5)	3(0,4)*
Endoscopy Score	5(1,6)	4(1,6)
Histology Score	2(2,6)	2(2,6)
Total Score (PDAI)	11(7,16)	9(2,16)*

*p<0.5 for within-group change. Baseline vs completion (signed rank test with two missing values at completion filled in by overall (groups) Baseline values).

Three patients had to discontinue treatment because of worsening of symptoms, but none developed dehydration or required hospitalization. Three patients had cramping discomfort in the pouch after taking the enema. One of the patients who developed cramps discontinued it because of the discomfort. One patient developed right lower abdominal pain and the study medication was discontinued.

The initial or final endoscopic or histologic scores of the patients are shown in Table 3.

In conclusion six of the twenty patients discontinued therapy and nine of fourteen patients (64%) who completed the treatment improved (defined as a reduction in the PDAI score of 3 points or more). This is particularly surprising in view of the fact that the patients were refractory to conventional therapy.

CLAIMS

1. Use of polysaccharide gum in the preparation of a medicament for the treatment of inflammatory bowel disease.

2. Use as claimed in Claim 1 wherein the disease state is pouchitis.

3. Use as claimed in Claim 1 wherein the polysaccharide gum is Xanthan gum.

4. Use as claimed in any one of Claims 1 to 3 wherein the medicament is a post-gastric delayed release oral composition or a rectally administrable composition.

5. Use as claimed in Claim 4 wherein the dosage of the polysaccharide per unit dose is 200mg to 2000mg.

6. Use as claimed in Claim 4 wherein the medicament is an enema or foam enema.

7. A post-gastrically delayed release oral or rectally administrable pharmaceutical composition comprising a polysaccharide gum as the sole therapeutically active agent together with a pharmaceutically acceptable carrier or vehicle.

8. A composition as claimed in Claim 7 which is further defined in accordance with Claims 3 to 6.

9. The use of a polysaccharide gum as the sole therapeutically active agent in the manufacture of a medicament for the treatment or prophylaxis of inflammatory bowel disease.